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1. Your reference: 96.79544

2. Patent application number *(The Patent Office will fill in this part)*: 0225655.0

05NOV02 E760829-6 D00027
P01/7700 0.00-0225655.0

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*:
Cambridge Consultants Limited
Science Park
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4 NOV 2002

Patents ADP number *(if you know it)*: 36161808 4

If the applicant is a corporate body, give country/state of incorporation: United Kingdom

4. Title of the invention: Pressurised Inhalers

5. Name of your agent *(if you have one)*:
Frank B. Dehn & Co.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*:
179 Queen Victoria Street
London
EC4V 4EL

Patents ADP number *(if you know it)*: 166001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
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Yes

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Continuation sheets of this form	0
Description	11
Claim(s)	0
Abstract	0
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Priority documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	0
Request for preliminary examination and search *(Patents Form 9/77)*	0
Request for substantive examination *(Patents Form 10/77)*	0
Any other documents *(please specify)*	No

11. I/We request the grant of a patent on the basis of this application.

Signature Date 4 November 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Adrian Samuels
01273 244200

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Pressurised Inhalers

This invention relates to pressurised canisters for metered dose inhalers, valves for such canisters and to the inhalers *per se*.

Aerosol technology has been in existence for nearly a century using propellants or pressurised gas to deliver a fine liquid spray. An important development of this technology was a valve which delivered a fixed volume of fluid for each single actuation of the device. This is described in US 22723055. It is fair to say that this development has revolutionised the drug delivery industry since fixed volumes of medication can be delivered using aerosol technology. This resulted in the advent of metered dose inhalers which are widely used today.

Metered dose inhalers have been used to treat asthma and other respiratory diseases for nearly 50 years and are currently the preferred method for delivering drugs to the lungs. However, there are a number of complications associated with the use of metered dose inhalers which limit their clinical effectiveness. Most significantly, there is a problem that standard inhaler devices require a degree of co-ordination on the part of the user that can make them difficult to use, particularly by certain groups of people such as the very young or very old. In particular, in order to use a metered dose inhaler correctly and successfully, the user must coordinate depressing the canister to dispense the dose with the first half of their inspiratory cycle. Failure to do this results in more limited quantities of the drug reaching the lungs than intended.

There have been many proposals in the prior art for overcoming this problem. The most elegant design of

such a device is shown in WO 93/24167 and is embodied in the marketed "Easibreath" device. Other proposals can be seen in US 5511540, WO 01/34231 and US 5347998.

Whilst the devices described above can help to alleviate the problem, they all require a large number of components in order to provide a mechanism which is sufficiently powerful to provide the relatively large force (typically of the order of 30 Newtons) required to actuate the canister, yet which is sufficiently sensitive to be triggered by the user's breath. This large number of components makes such devices expensive and there is, therefore, a general reluctance to adopt them as standard drug delivery devices.

Another disadvantage in known metered dose inhalers is that users are advised to waste the first dose from the device when it has been unused for a significant period of time. The reason for this is that after each actuation, the return stroke of the nozzle causes a metering chamber within the canister to be refilled with the next dose. However, over a long period of time, there is a tendency for the active ingredient in the isolated dose to migrate out of the metering chamber thus reducing the net concentration of active ingredient and consequently reducing the therapeutic benefit of the dose held in the metering chamber.

Finally, the fact that a dose is always isolated in the metering chamber ready for dispensing in the next actuation, means that shaking the canister in order to obtain an even mix of propellant and active ingredient, as users are recommended to do, will be ineffective for the dose which will be next delivered.

It is the object of the present invention to alleviate the problems set out above. When viewed from a first aspect the invention provides a pressurised canister for a metered dose inhaler comprising a resiliently biased nozzle and arranged to dispense a metered dose of fluid from said nozzle upon releasing

the nozzle from its depressed condition.

Thus it will be seen by those skilled in the art that the present invention represents a complete departure from the accepted assumption in the art that the dose is always delivered by pressing the nozzle. The Applicants now appreciate that there are several advantages arising from arranging the to dispense the mixture of propellant and active ingredient upon the release stroke of the actuation of the nozzle rather than the initial depression stroke. One of the advantages of this arrangement is that it has been found that it is significantly easier for a human user to coordinate releasing the force required to actuate the nozzle of a canister with inhalation than it is to coordinate applying such force with inhalation. Thus, the user may provide the force to depress the nozzle into the canister without any coordination and then coordinate releasing the canister with inhalation.

More importantly, however, the reduced force required to release rather than to apply the actuation force means that a much more straightforward latch mechanism, operated directly by the user's in-breath, may be provided. The invention therefore also extends to an inhaler device comprising means for latching a canister in its depressed condition and means for releasing said latch upon inhalation by a user.

As well as the advantage of improving user coordination, in accordance with the invention, the Applicants have further realised that dispensing the dose in the second, release half of the actuation cycle makes it easy to arrange for the does to be isolated during the same actuation cycle as it is dispensed. This has two main advantages. The first is that in normal use the dose to be dispensed will only be isolated for a very short period of time and there will therefore be insufficient time for the active ingredient to migrate out of it. This removes the need for a user

to waste the first dose from the canister after it has not been used for a long period of time.

Secondly, the canister may be shaken prior to actuation, i.e. before the dose is isolated, which will result in a homogenous dose being dispensed. This reduces the risk of poor dose content uniformity.

When viewed from a second aspect, therefore, the present invention provides a pressurised canister for delivering a metered dose of fluid therefrom comprising a resiliently biased nozzle and arranged to isolate and deliver the same dose in a single actuation cycle. In other words, in each cycle of depressing and releasing the nozzle, a predetermined dose is isolated from the contents of the canister and dispensed from the nozzle.

It is envisaged that the dose may be isolated and dispensed during the same half of the actuation cycle. For example, the dose could be both isolated and dispensed on the depression stroke or, more preferably, isolated and dispensed on the release stroke. Most preferably, however, the dose is isolated during the depression stroke and dispensed during the release stroke. The advantages of dispensing during the release stroke for improving the ability to coordinate with breathing in are given above. The advantage of having the dose isolated in the other half of the cycle is that in general this arrangement minimises the length of stroke required.

It should be appreciated that although the present specification refers to isolating a dose, it should not be taken to imply that the isolated dose is sealed from the bulk of the canister's contents. It is sufficient that a predetermined volume of mixture is physically separated in some way from the remainder.

Many straightforward ways of implementing the arrangements set out above may be envisaged. In a preferred set of embodiments for example, the canister comprises a valve including a metering chamber and a

hollow nozzle resiliently biased into a first position in which said nozzle is in fluid communication with the metering chamber, said nozzle being moveable against said resilient bias to a second position in which the metering chamber is in fluid communication with the interior of the canister. It will also be appreciated that the invention extends to a valve for a canister said valve comprising a metering chamber, an inlet for fluidly communicating with the interior of a canister and a hollow nozzle resiliently biased into a first position in which the nozzle is in fluid communication with the metering chamber, but moveable against said resilient bias into a second position in which the inlet is in fluid communication with the metering chamber.

Indeed, it will be appreciated that in general the invention extends to valves *per se* for pressurised canisters having the features of the canisters described hereinabove in accordance with the invention. When viewed from another aspect therefore the invention provides a valve for a pressurised canister, comprising a resiliently biased nozzle, the valve being arranged to dispense a metered dose of fluid from said nozzle upon releasing the nozzle from its depressed condition.

When viewed from a yet further aspect the invention provides a valve for a pressurised canister comprising a resiliently biased nozzle, said valve being arranged to isolate and deliver the same metered dose of fluid in a single actuation cycle.

A preferred embodiment of the invention will now be described, by way of example only, with reference to the accompanying drawings in which:

Figure 1 is a partially cut-away perspective view of a pressurised canister and its valve in accordance with the invention;

Figure 2 is a close-up view of the valve of Figure 1;

Figure 3 is a view similar to Figure 1 in which the

nozzle is depressed; and

Figure 4 is a sectional view through an inhaler in accordance with a further aspect of the invention.

Turning to Figure 1, there may be seen a valve arrangement 2 provided at one end of a sealed canister 4. The valve mechanism 2 is retained in the end of the canister 4 by a sealing cap 6 as is well known in the art. The valve mechanism 2 has a hollow nozzle 8 extending along the axis of the canister 4 and through an aperture in the sealing cap 6.

The housing of the valve mechanism is generally bell-shaped with a wide base flange 10a abutting the under-side of the sealing cap, a main body section 10b and a narrower end neck portion 10c. The shape of the canister in the region of the ceiling cap 6 is such that when the cap 6 is applied, the base flange 10a of the valve mechanism is clamped between the body of the canister 4 and the underside of the cap 6. A washer seal 12 forms a pressure-tight seal around the aperture in the cap 6 for the nozzle 8.

Turning now to Figure 2 in which the valve mechanism may be seen in more detail, it will be seen that the nozzle member 8 is a sliding fit inside the narrowed end neck portion 10c of the valve and also in the main body portion 10b as a result of a radially extending flange 14 provided part-way along the nozzle member 8.

The innermost end of the nozzle member 8 is formed with a narrow tapered head 16 defining a shoulder 18 where it joins the rest of the nozzle member 8. A compression coil spring 20 is disposed between the shoulder 18 of the nozzle member and the inner end of the neck portion 10c of the valve so as to encircle the tapered head 16. The spring 20 acts to bias the nozzle member 8 towards the front end of the valve mechanism 2 so that its radial flange 14 abuts against the washer seal 12.

Two further washer seals 22, 24 are provided around the nozzle member 8 within the main body 10b of the valve to seal against the outside of the nozzle member 8 and the inside of the valve casing 10b respectively. One of the seals 22 abuts against the inside of the shoulder formed between the main body 10b and the narrowed end neck portion 10c of the valve. The second seal 24 is spaced axially from the first. The two seals 22,24 are fixed in their axial positions by a pair of L-section spacers 26,28 which are themselves a tight interference fit in the main section 10b of the valve body. The two seals 22,24 define between them a metering chamber 30 of precise predetermined volume having the shape of a rectangular-section toroid. The metering chamber 30 is in fluid communication with the axial bore 32 of the nozzle member 8 through a radial bore section 34.

On the other side of the foremost seal 24 a larger chamber 36 is defined. An aperture 38 through the wall of the main valve body 10b is provided so that the chamber 36 is in fluid communication with the interior of the canister 4.

A notch 40 is cut out of the part of the nozzle member 8 which is disposed in the larger chamber 36 in the configuration shown in Fig. 2.

Operation of the valve will now be described with reference to Figures 1-3. The normal rest state of the valve mechanism is shown in Figures 1 and 2. The canister 4 is filled with a mixture of pressurised propellant and active ingredient. The aperture 38 in the body 10b of the valve means that the propellant/drug mix fills the larger fore-chamber 36 of the valve. The metering chamber 30 on the other hand is empty and at atmospheric pressure since it is open to the atmosphere through the bores 32, 34 of the nozzle member 8.

When it is desired to dispense a dose of drug from the canister, the nozzle 8 is depressed into the

canister 4 against the force of the coil spring 20. This is shown in Figure 3. In the fully depressed condition, the tip of the tapered head 16 at the end of the nozzle member 8 abuts against the inner wall of the valve neck portion 10c. In this position, the nozzle 8 is moved sufficiently far into the valve that the notch 40 in the side of the nozzle member 8 is aligned with the foremost seal 24 which defines one side of the metering chamber 30. This allows the pressurised propellant/drug mix to bypass the seal 24 to enter and fill the metering chamber 30. The volume of the metering chamber 30 is precisely predetermined to isolate the required dose. It will of course be appreciated that in the depressed condition, the metering chamber 30 is closed to the atmosphere since the radial bore 34 of the nozzle member is no longer in alignment with it.

When pressure on the nozzle member 8 is released, the spring 20 returns it to its original position as shown in Figures 1 and 2. During the first part of this movement, the notch 40 is moved out from under the seal 24 in order to reseal the metering chamber 30. Thereafter, the radial bore 34 in the nozzle member 8 is once again brought into alignment with the metering chamber 30 thus opening the metering chamber 30 to the atmosphere. Since the pressure of the propellant in the metering chamber 30 is significantly elevated above atmospheric pressure, this will cause the propellant/drug mix to be sprayed from the end of the nozzle 8 as is well known in the art.

Thus, it will be appreciated by those skilled in the art that during a single actuation cycle of depressing and subsequently releasing the nozzle 8, a dose of propellant and drug is isolated in the metering chamber 30 and the same dose is then dispensed. This means that the canister 4 may be shaken prior to actuation to achieve a homogenous mix of drug and

propellant throughout, from which a dose of the correct concentration can be isolated. Furthermore, since the nozzle would normally be released very shortly after it is depressed, there is insufficient time for the active ingredient to migrate out of the metering chamber 30.

Moreover, in the fully depressed condition shown in Figure 3, although a dose is isolated in the metering chamber 30, the bypass notch 40 under the seal 24 means that the chamber 30 is not sealed against the interior of the canister 4. Thus, even if the nozzle were to remain in its depressed condition for a relatively prolonged period of time, migration of the active ingredient is unlikely to be a significant problem. Indeed, the contents of the metering chamber is in fact only completely sealed for a fraction of a second during the release stroke between the time when the notch 40 and the radial bore 34 of the nozzle are respectively aligned with the metering chamber 34. It will be appreciated from this that it is not necessary to waste a dose from the canister even if it has not been used for a long time.

Figure 4 shows schematically a cross-section through an inhaler in accordance with a further aspect of the invention. The inhaler 50 comprises generally an approximately vertical canister holster portion 52 and a horizontal mouth-piece portion 54. The holster portion 52 receives the canister 4 described above with reference to Figures 1-3, although any canister in accordance with the principles set out herein may be used.

The nozzle 8 of the canister is received in a seat member 56 having a flared outlet 58 from which the pressurised propellant and drug mixture will be sprayed into the mouth-piece 54 when dispensed from the canister 4.

The novel feature of the inhaler is a latch mechanism comprising a pivotally mounted latch arm 60

and a hinged flap 62. The latch arm 60 is pivoted approximately half way along its length and has a pointed nose 64 at one end. The flap 62 is hinged about its upper edge. The upper edge is formed as a rounded cam surface 66.

In use, the nozzle 8 extends out of the canister 4 by its maximum amount so that the cap 6 of the canister is located above the pointed nose 64 of the latch arm 60 (not shown). When the user wishes to dispense and inhale a dose of drug from the canister, he or she first depresses the top of the canister 4 downwardly relatively to the inhaler 50. This causes the nozzle 8 to be depressed into the canister 4. As was explained above with reference to Figures 1 to 3, this does not cause a dose to be dispensed from the canister but does isolate a dose ready for dispensing. It is not therefore required to coordinate this action with any breathing.

As the body of the canister 4 moves downwardly, the sealing cap 6 is forced past the pointed nose 64 on the latch arm 60 which is held against the canister by the cam surface 66 bearing onto its opposite end. The nose 64 is thus hooked over the cap 6 and retains the canister 4 in its depressed condition. This is the condition shown in Figure 4. The inhaler is now primed for dispensing the dose.

When the user is ready, he or she may then place his or her lips around the outside of the mouth-piece 54 and inhale. The subsequent movement of air through the inhaler 50 causes the flap 62 to rotate upwardly in a clockwise direction (as viewed from Figure 4). The resulting movement of the cam surface 66 at the top of the flap 62 releases the latch arm 60 and so allows the pointed nose 64 to disengage from the cap 6. This causes the canister to return to its original position under the force stored in the spring of its valve. As will be appreciated from the description above, this

causes a dose of drug and propellant to be dispensed from the canister's nozzle 8 and sprayed from the outlet 58 into the mouth-piece 54, therefore allowing it to be inhaled into the user's lungs. Thus, it will be appreciated that the user does not need to coordinate any action with his or her in-breath since the inhalation automatically causes the dose to be dispensed. The latch mechanism may be as simple as shown since only a relatively small force is required to disengage the latch and therefore release the previously stored energy from the canister valve. This small release force can easily be provided by the user's in-breath.

It will be appreciated by those skilled in the art that the embodiments described above are only specific examples of how the principles of the invention may be implemented and there are many possible variants within the scope of the invention.

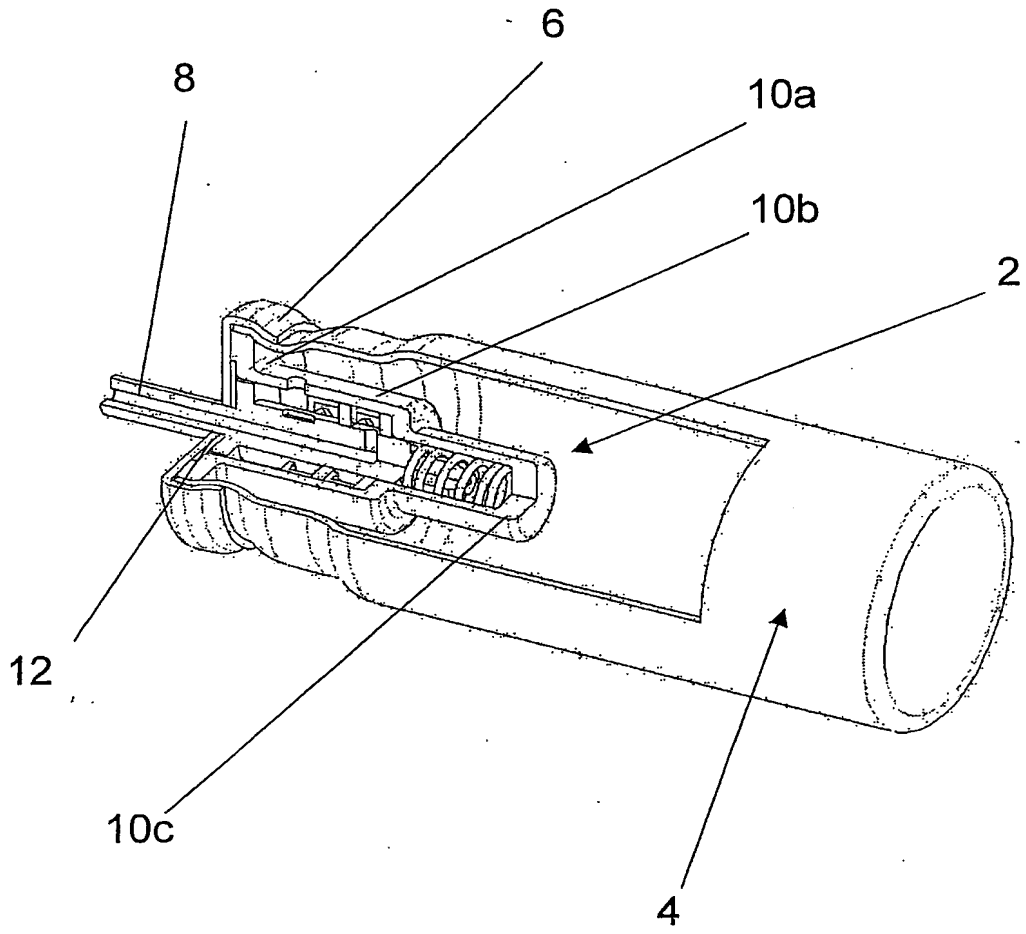

FIG 1

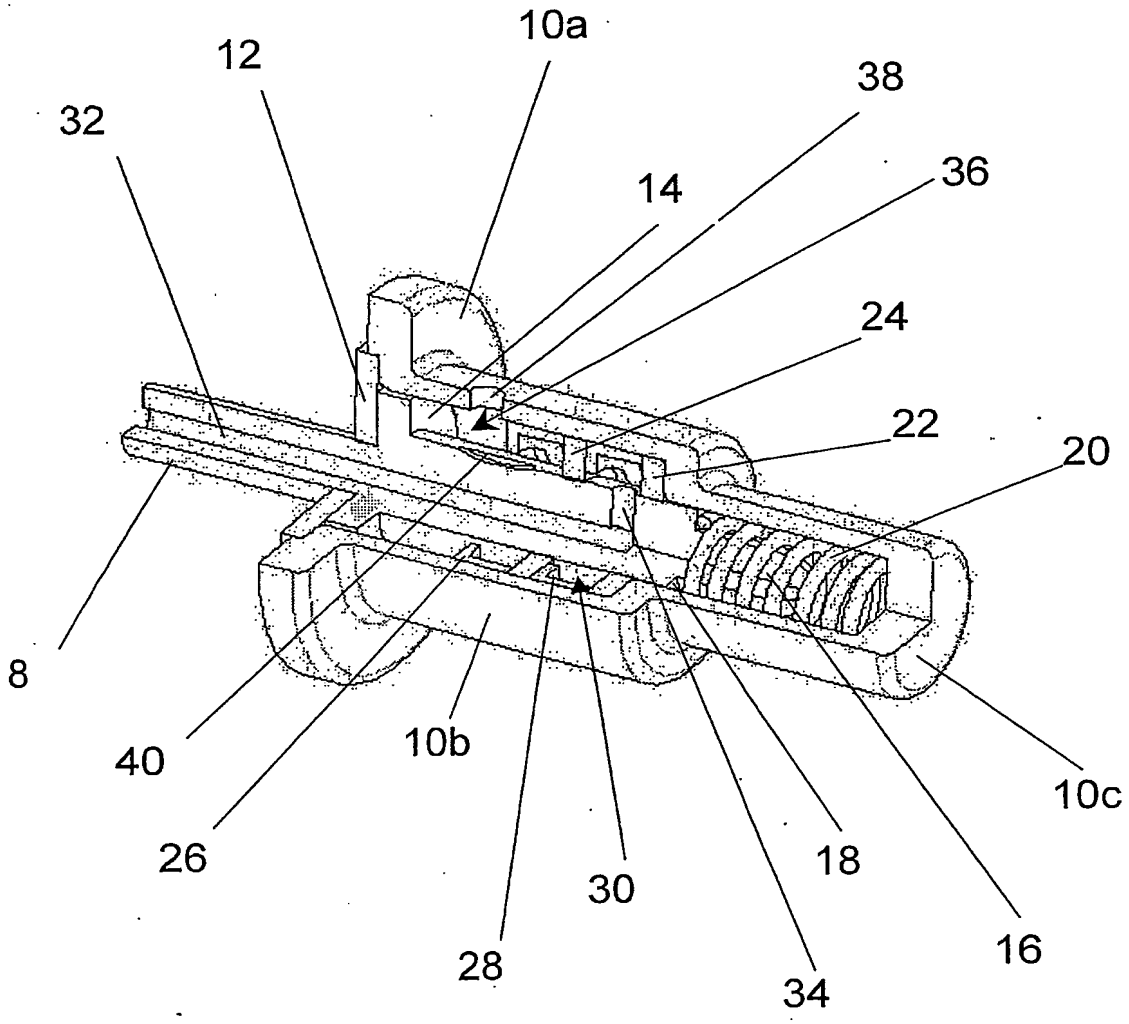

FIG 2

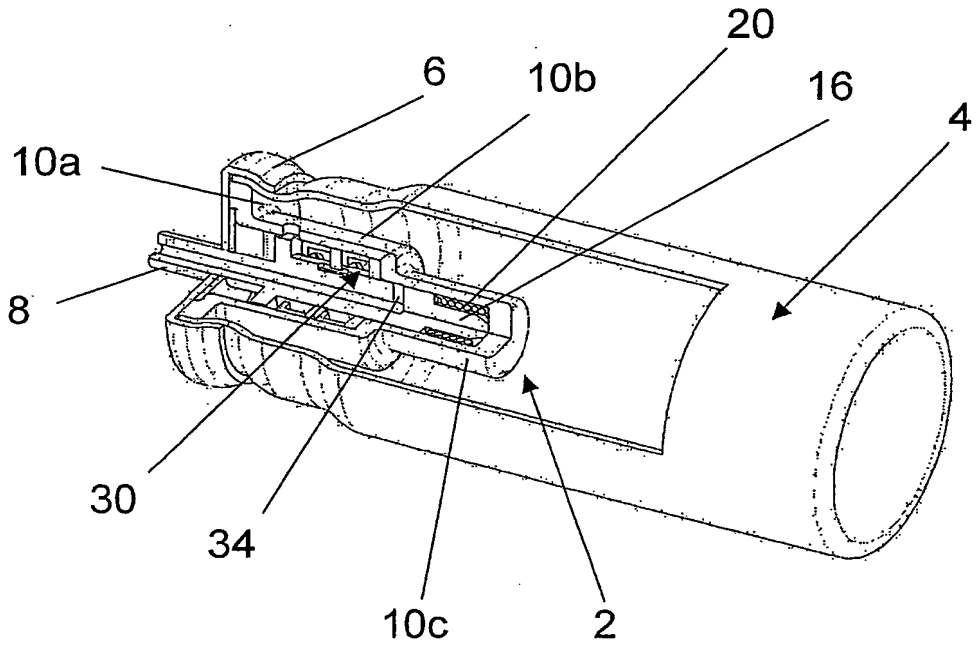

FIG 3

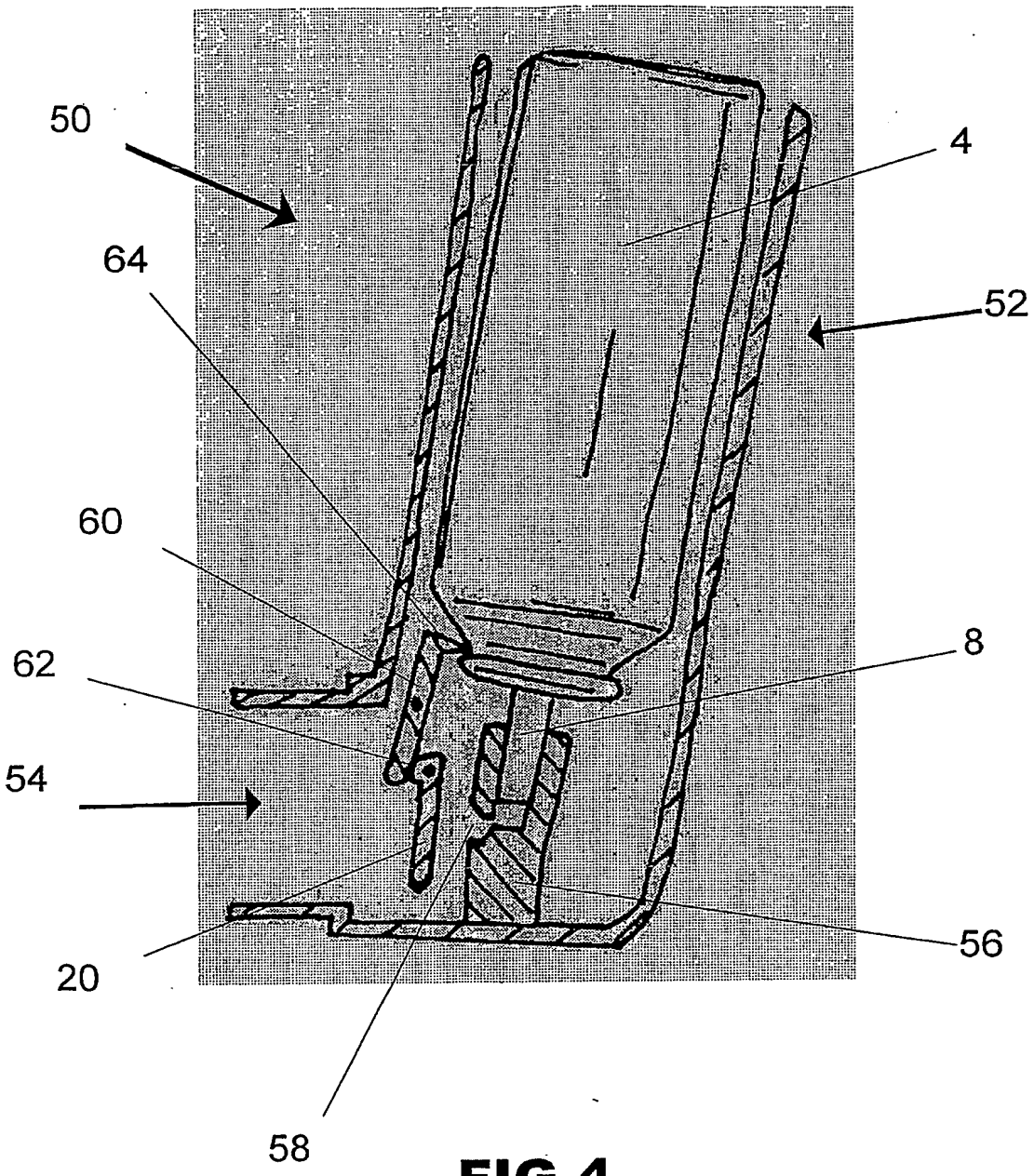

FIG 4

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